

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: : 050759

FINAL PRINTED LABELING

(Roche Hexagon)

CellCept®

(mycophenolate mofetil capsules)

(mycophenolate mofetil tablets)

CellCept® Oral Suspension

(mycophenolate mofetil for oral suspension)

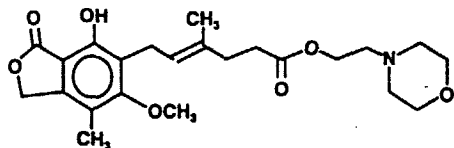
CellCept® Intravenous

(mycophenolate mofetil hydrochloride for injection)

WARNING: Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal or cardiac transplant patients should use CellCept. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION: CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent.

The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula:



Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 $\mu\text{g/mL}$ at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W). The pH of the reconstituted solution is 2.4 to 4.1.

CellCept is available for oral administration as capsules containing 250 mg of mycophenolate mofetil, tablets containing 500 mg of mycophenolate mofetil and as a powder for oral suspension, which when constituted contains 200 mg/mL mycophenolate mofetil.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Inactive ingredients in CellCept 250 mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide and yellow iron oxide.

Inactive ingredients in CellCept 500 mg tablets include black iron oxide, croscarmellose sodium, FD&C blue #2 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone (K-90), red iron oxide, talc and titanium dioxide; may also contain ammonium hydroxide, ethyl alcohol, methyl alcohol, n-butyl alcohol, propylene glycol and shellac.

Inactive ingredients in CellCept Oral Suspension include aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin and xanthan gum.

CellCept Intravenous is the hydrochloride salt of mycophenolate mofetil. The chemical name for the hydrochloride salt of mycophenolate mofetil is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride. It has an empirical formula of $C_{23}H_{31}NO_7 \cdot HCl$ and a molecular weight of 469.96.

CellCept Intravenous is available as a sterile white to off-white lyophilized powder in vials containing mycophenolate mofetil hydrochloride for administration by intravenous infusion only. Each vial of CellCept Intravenous contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt. The inactive ingredients are polysorbate 80, 25 mg, and citric acid, 5 mg. Sodium hydroxide may have been used in the manufacture of CellCept Intravenous to adjust the pH. Reconstitution and dilution with 5% Dextrose Injection USP yields a slightly yellow solution of mycophenolate mofetil, 6 mg/mL. (For detailed method of preparation, see DOSAGE AND ADMINISTRATION.)

CLINICAL PHARMACOLOGY:

Mechanism of Action: Mycophenolate mofetil has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets and bone marrow).

Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and heart allografts in rats, as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies. Mycophenolate mofetil has been demonstrated to inhibit immunologically-mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Pharmacokinetics: Following oral and IV administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The parent drug, mycophenolate mofetil, can be measured systemically during the intravenous infusion; however, shortly (about 5 minutes) after the infusion is stopped or after oral administration, MMF concentration is below the limit of quantitation (0.4 µg/mL).

Absorption: In 12 healthy volunteers, the mean absolute bioavailability of oral mycophenolate mofetil relative to IV mycophenolate mofetil (based on MPA AUC) was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g (see table below on pharmacokinetic parameters in renal and cardiac transplant patients).

The C_{max} and AUC of MPA in early transplant patients (<40 days posttransplant) are approximately 45% to 50% and 20% to 30% lower, respectively, as compared to healthy volunteers or to stable renal and cardiac transplant patients.

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g bid to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food (see DOSAGE AND ADMINISTRATION).

Distribution: The mean (±SD) apparent volume of distribution of MPA in twelve healthy volunteers is approximately 3.6 (±1.5) and 4.0 (±1.2) L/kg following IV and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

In vitro studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with HSA) and MPAG (at ≥ 460 $\mu\text{g/mL}$ with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 $\mu\text{g/mL}$ had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

Metabolism: Following oral and intravenous dosing, mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of mycophenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in approximately a 40% decrease in the MPA AUC (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about three- to six-fold increase) are observed in patients with renal insufficiency (see CLINICAL PHARMACOLOGY: *Special Populations*).

Excretion: Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 $\mu\text{g/mL}$), small amounts of MPAG are removed.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Mean (\pm SD) apparent half-life and plasma clearance of MPA are 17.9 (\pm 6.5) hours and 193 (\pm 48) mL/min following oral administration and 16.6 (\pm 5.8) hours and 177 (\pm 31) mL/min following IV administration, respectively.

Pharmacokinetics in Healthy Volunteers, Renal and Cardiac Transplant Patients: Shown below are the mean (\pm SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal and cardiac transplant patients. After oral dosing the C_{\max} and AUC of MPA in early transplant patients (<40 days posttransplant) are approximately 45% to 50% and 20% to 30% lower, respectively, as compared to healthy volunteers or to stable renal and cardiac transplant patients. Mean MPA AUC values following administration of 1 g bid intravenous mycophenolate mofetil over 2 hours to patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate posttransplant phase.

Pharmacokinetic Parameters for MPA
[mean (\pm SD)]
Following Administration of Mycophenolate Mofetil
to Healthy Volunteers (Single Dose),
Renal and Cardiac Transplant Patients (Multiple Doses)

	Dose/ Route	T_{\max} (h)	C_{\max} (μ g/mL)	Total AUC (μ g·h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (\pm 0.36) (n=129)	24.5 (\pm 9.5) (n=129)	63.9 (\pm 16.2) (n=117)
Renal Transplant Patients (bid dosing) Time After Transplantation	Dose/ Route	T_{\max} (h)	C_{\max} (μg/mL)	Interdosing Interval AUC₀₋₁₂ (μg·h/mL)
5 days	1 g/ iv	1.58 (\pm 0.46) (n=31)	12.0 (\pm 3.82) (n=31)	40.8 (\pm 11.4) (n=31)
6 days	1g/ oral	1.33 (\pm 1.05) (n=31)	10.7 (\pm 4.83) (n=31)	32.9 (\pm 15.0) (n=31)
Early (<40 days)	1 g/ oral	1.31 (\pm 0.76) (n=25)	8.16 (\pm 4.50) (n=25)	27.3 (\pm 10.9) (n=25)

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Early (<40 days)	1.5 g/ oral	1.21 (±0.81) (n=27)	13.5 (±8.18) (n=27)	38.4 (±15.4) (n=27)
Late (>3 months)	1.5 g/ oral	0.90 (±0.24) (n=23)	24.1 (±12.1) (n=23)	65.3 (±35.4) (n=23)
Cardiac Transplant Patients (bid dosing) Time After Transplantation	Dose/ Route	T_{max} (h)	C_{max} (µg/mL)	Interdosing Interval AUC₀₋₁₂ (µg·h/mL)
Early (Day before discharge)	1.5 g/ oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=9)
Late (>6 months)	1.5 g/ oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1* (±20.4) (n=49)

* AUC₀₋₁₂ values quoted are extrapolated from data from samples collected over 4 hours.

Two 500 mg tablets have been shown to be bioequivalent to four 250 mg capsules.

5 mL of the 200 mg/mL constituted suspension have been shown to be bioequivalent to four 250 mg capsules.

Special Populations: Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to non-transplant subjects with renal or hepatic impairment.

Pharmacokinetic Parameters for MPA

[mean (±SD)]

Following Single Doses of Mycophenolate Mofetil Capsules in Chronic Renal and Hepatic Impairment

Renal Impairment (no. of patients)	Dose	T_{max} (h)	C_{max} (µg/mL)	AUC₀₋₉₆ (µg·h/mL)
Healthy Volunteers GFR >80 mL/min/1.73 m ² (n=6)	1 g	0.75 (±0.27)	25.3 (±7.99)	45.0 (±22.6)
Mild Renal Impairment GFR 50 to 80 mL/min/1.73 m ² (n=6)	1 g	0.75 (±0.27)	26.0 (±3.82)	59.9 (±12.9)

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 m ² (n=6)	1 g	0.75 (±0.27)	19.0 (±13.2)	52.9 (±25.5)
Severe Renal Impairment GFR <25 mL/min/1.73 m ² (n=7)	1 g	1.00 (±0.41)	16.3 (±10.8)	78.6 (±46.4)
Hepatic Impairment (no. of patients)	Dose	T_{max} (h)	C_{max} (µg/mL)	AUC₀₋₄₈ (µg·h/mL)
Healthy Volunteers (n=6)	1 g	0.63 (±0.14)	24.3 (±5.73)	29.0 (±5.78)
Alcoholic cirrhosis (n=18)	1 g	0.85 (±0.58)	22.4 (±10.1)	29.8 (±10.7)

Renal Insufficiency: In a single-dose study, MMF was administered as capsule or intravenous infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73 m²] was about 75% higher relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 m²). In addition, the single-dose plasma MPAG AUC was three- to six-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Plasma MPA AUC observed after single dose (1 g) intravenous dosing to volunteers (n=4) with severe chronic renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73m²] was 62.4 µg·h/mL (±19.3). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied (see PRECAUTIONS: *General* and DOSAGE AND ADMINISTRATION).

In patients with delayed renal graft function posttransplant, mean MPA AUC₀₋₁₂ was comparable to that seen in posttransplant patients without delayed graft function. Mean plasma MPAG AUC₀₋₁₂ was two- to three-fold higher than in posttransplant patients without delayed graft function (see PRECAUTIONS: *General* and DOSAGE AND ADMINISTRATION).

The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (>100 µg/mL), hemodialysis removes only small amounts of MPAG.

Hepatic Insufficiency: In a single-dose (1 g, oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies may show a different effect. In a single-dose (1 g) intravenous study of 6 volunteers with alcoholic cirrhosis, MPA AUC was 44.1 $\mu\text{g}\cdot\text{h}/\text{mL}$ (± 15.5).

Pediatrics: Very limited pharmacokinetic data are available for pediatric renal transplant recipients. Data on these patients are presented in the table below:

Pharmacokinetic Parameters for MPA
[mean \pm (SD)]
Following Multiple Oral Doses of
Mycophenolate Mofetil in Pediatric Renal Transplant Patients
21 Days Posttransplant

Age Range	Dose	T _{max} (h)	C _{max} ($\mu\text{g}/\text{mL}$)	AUC ₀₋₁₂ ($\mu\text{g}\cdot\text{h}/\text{mL}$)
≥ 3 mo to <6 yr (Mean = 2.75) (n=4)	15 mg/kg bid	1.25 (± 0.87)	3.70 (± 2.08)	13.6 (± 8.69)
≥ 6 yr to <12 yr (Mean = 9.0) (n=4)	15 mg/kg bid	0.50 (± 0.00)	13.5 (± 4.48)	23.4 (± 2.84)
≥ 12 yr to 18 yr (Mean = 15.6) (n=5)	15 mg/kg bid	0.50 (± 0.00)	13.2 (± 6.86)	30.0 (± 8.34)
≥ 6 yr to <12 yr (Mean = 9.8) (n=5)	23 mg/kg bid	1.46 (± 0.79)	17.0 (± 20.0)	40.1 (± 17.6)
≥ 12 yr to 18 yr (Mean = 14.6) (n=6)	23 mg/kg bid	1.32 (± 0.76)	11.5 (± 10.2)	31.1 (± 11.4)

Gender: Data obtained from several studies were pooled to look at any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (\pm SD) MPA AUC₀₋₁₂ for males (n=79) was 32.0 (± 14.5) and for females (n=41) was 36.5 (± 18.8) $\mu\text{g}\cdot\text{h}/\text{mL}$ while mean (\pm SD) MPA C_{max} was 9.96 (± 6.19) in the males and 10.6 (± 5.64) $\mu\text{g}/\text{mL}$ in the females. These differences are not of clinical significance.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

CLINICAL STUDIES: The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in renal transplant patients in three randomized, double-blind, multicenter trials and in cardiac patients in one randomized double-blind, multicenter trial.

Renal Transplant: These three studies compared two dose levels of oral CellCept (1 g bid and 1.5 g bid) with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporine (Sandimmune®) and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®) induction therapy. These studies are described by geographic location of the investigational sites. One study was conducted in the USA at 14 sites, one study was conducted in Europe at 20 sites, and one study was conducted in Europe, Canada, and Australia at a total of 21 sites.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). CellCept, when administered with antithymocyte globulin (ATGAM®) induction (one study) and with cyclosporine and corticosteroids (all three studies), was compared to the following three therapeutic regimens: (1) antithymocyte globulin (ATGAM®) induction/azathioprine/cyclosporine/corticosteroids, (2) azathioprine/cyclosporine/corticosteroids, and (3) cyclosporine/corticosteroids.

CellCept, in combination with corticosteroids and cyclosporine reduced (statistically significant at the <0.05 level) the incidence of treatment failure within the first 6 months following transplantation. The following tables summarize the results of these studies. These tables show (1) the proportion of patients experiencing treatment failure, (2) the proportion of patients who experienced biopsy-proven acute rejection on treatment, and (3) early termination, for any reason other than graft loss or death, without a prior biopsy-proven acute rejection episode. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarized separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients discontinued receiving CellCept (without prior biopsy-proven rejection, death or graft loss) than discontinued in the control groups, with the highest rate in the CellCept 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in the CellCept 3 g/day group.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Renal Transplant Studies
Incidence of Treatment Failure
(Biopsy-proven Rejection or Early Termination for Any Reason)

USA Study (N=499 patients)	CellCept 2 g/day (n=167 patients)	CellCept 3 g/day (n=166 patients)	Azathioprine 1 to 2 mg/kg/day (n=166 patients)
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection*	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%
Europe/Canada/ Australia Study (N=503 patients)	CellCept 2 g/day (n=173 patients)	CellCept 3 g/day (n=164 patients)	Azathioprine 100 to 150 mg/day (n=166 patients)
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection*	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study (N=491 patients)	CellCept 2 g/day (n=165 patients)	CellCept 3 g/day (n=160 patients)	Placebo (n=166 patients)
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection*	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

* Does not include death and graft loss as reason for early termination.

Cumulative incidence of 12-month graft loss and patient death are presented below. No advantage of CellCept with respect to graft loss and patient death was established. Numerically, patients receiving CellCept 2 g/day and 3 g/day experienced a better outcome than controls in all three studies; patients receiving CellCept 2 g/day experienced a better outcome than CellCept 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss and patient death at 1 year.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

**Renal Transplant Studies
Cumulative Incidence of Combined Graft Loss
and Patient Death at 12 Months**

Study	CellCept 2 g/day	CellCept 3 g/day	Control (Azathioprine or Placebo)
USA	8.5%	11.5%	12.2%
Europe/Canada/Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

Cardiac Transplant: A double-blind, randomized, comparative, parallel-group, multicenter study in primary cardiac transplant recipients was performed at 20 centers in the United States, one in Canada, five in Europe and two in Australia. The total number of patients enrolled was 650; 72 never received study drug and 578 received study drug. Patients received CellCept 1.5 g bid (n=289) or azathioprine 1.5 to 3 mg/kg/day (n=289), in combination with cyclosporine (Sandimmune® or Neoral®) and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with hemodynamic compromise, or were retransplanted or died, within the first 6 months, and (2) the proportion of patients who died or were transplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

(1) *Rejection:* No difference was established between CellCept and azathioprine (AZA) with respect to biopsy-proven rejection with hemodynamic compromise, as presented below.

Rejection at 6 Months

	All Patients		Treated Patients	
	AZA N = 323	CellCept N = 327	AZA N = 289	CellCept N = 289
Biopsy-proven rejection with hemodynamic compromise*	121 (38%)	120 (37%)	100 (35%)	92 (32%)

* Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥ 20 mm or a 25% increase; cardiac index < 2.0 l/min/m² or a 25% decrease; ejection fraction $\leq 30\%$; pulmonary artery oxygen saturation $\leq 60\%$ or a 25% decrease; presence of new S₃ gallop; fractional shortening was $\leq 20\%$ or a 25% decrease; inotropic support required to manage the clinical condition.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

(2) *Survival*: CellCept was shown to be at least as effective as AZA in preventing death or retransplantation at 1 year, as presented below.

Death or Retransplantation at 1 Year

	All Patients		Treated Patients	
	AZA N = 323	CellCept N = 327	AZA N = 289	CellCept N = 289
Death or Retransplantation	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)

INDICATIONS AND USAGE: *Renal and Cardiac Transplant*: CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants and in patients receiving allogeneic cardiac transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

CONTRAINDICATIONS: Allergic reactions to CellCept have been observed; therefore, CellCept is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. CellCept Intravenous is contraindicated in patients who are allergic to Polysorbate 80 (TWEEN).

WARNINGS (see boxed WARNING): Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Oversuppression of the immune system can also increase susceptibility to infection.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

CellCept has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM®), OKT3 (Orthoclone OKT® 3), cyclosporine (Sandimmune®, Neoral®) and corticosteroids. The efficacy and safety of the use of CellCept in combination with other immunosuppressive agents have not been determined.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Lymphoproliferative disease or lymphoma developed in approximately 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal and cardiac transplant patients (see ADVERSE REACTIONS).

Adverse effects on fetal development (including malformations) occurred when pregnant rats and rabbits were dosed during organogenesis. These responses occurred at doses lower than those associated with maternal toxicity, and at doses below the recommended clinical dose for renal or cardiac transplantation. There are no adequate and well-controlled studies in pregnant women. However, as CellCept has been shown to have teratogenic effects in animals, it may cause fetal harm when administered to a pregnant woman. Therefore, CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is recommended that CellCept therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.

Effective contraception must be used before beginning CellCept therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy (see PRECAUTIONS: *Pregnancy and Information for Patients*).

In controlled studies for prevention of renal or cardiac rejection, similar rates of fatal infection/sepsis (<2%) occurred in patients receiving CellCept (2 g or 3 g) (see ADVERSE REACTIONS).

Severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu\text{L}$] developed in up to 2.0% of renal transplant patients and up to 2.8% of cardiac transplant patients receiving CellCept (see ADVERSE REACTIONS). Patients receiving CellCept should be monitored for neutropenia (see PRECAUTIONS: *Laboratory Tests*). The development of neutropenia may be related to CellCept itself, concomitant medications, viral infections, or some combination of these causes. If neutropenia develops (ANC $<1.3 \times 10^3/\mu\text{L}$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see DOSAGE AND ADMINISTRATION). Neutropenia has been observed most frequently in the period from 31 to 180 days posttransplant in patients treated for prevention of renal and cardiac rejection.

Patients receiving CellCept should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

PRECAUTIONS: General: Gastrointestinal hemorrhage has been observed in approximately 3% of renal transplant patients and in 2.8% of cardiac transplant patients treated with CellCept 3 g daily. Gastrointestinal perforations have rarely been observed. Most patients receiving CellCept were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate mofetil. Because CellCept has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, CellCept should be administered with caution in patients with active serious digestive system disease.

Subjects with severe chronic renal impairment ($\text{GFR} < 25 \text{ mL/min/1.73 m}^2$) who have received single doses of CellCept showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of CellCept greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and DOSAGE AND ADMINISTRATION).

No data are available for cardiac transplant patients with severe chronic renal impairment. CellCept may be used for cardiac transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

In patients with delayed renal graft function posttransplant, mean MPA AUC_{0-12} was comparable, but MPAG AUC_{0-12} was two- to three-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. In the three controlled studies of prevention of renal rejection, there were 298 of 1483 patients (20%) with delayed graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and DOSAGE AND ADMINISTRATION).

It is recommended that CellCept not be administered concomitantly with azathioprine because such concomitant administration has not been studied clinically.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of CellCept with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of CellCept (see PRECAUTIONS: *Drug Interactions*).

Phenylketonurics: CellCept Oral Suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine per mL suspension).

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Information for Patients: Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving CellCept. Patients should be given complete dosage instructions and informed of the increased risk of lymphoproliferative disease and certain other malignancies. Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning CellCept therapy, during therapy and for 6 weeks after CellCept has been stopped (see WARNINGS and PRECAUTIONS: *Pregnancy*).

Laboratory Tests: Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year (see WARNINGS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION).

Drug Interactions: Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, and trimethoprim/sulfamethoxazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal or cardiac transplant patients. CellCept has not been administered concomitantly with azathioprine.

Acyclovir: Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to twelve healthy volunteers resulted in no significant change in MPA AUC and C_{max} . However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for the two drugs to compete for tubular secretion, further increasing the concentrations of both drugs.

Antacids With Magnesium and Aluminum Hydroxides: Absorption of a single dose of mycophenolate mofetil (2 g) was decreased when administered to ten rheumatoid arthritis patients also taking Maalox® TC (10 mL qid). The C_{max} and AUC₀₋₂₄ for MPA were 33% and 17% lower, respectively, than when mycophenolate mofetil was administered alone under fasting conditions. CellCept may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that CellCept and the antacid not be administered simultaneously.

Cholestyramine: Following single-dose administration of 1.5 g mycophenolate mofetil to twelve healthy volunteers pretreated with 4 g tid of cholestyramine for 4 days, MPA AUC decreased approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following IV administration of CellCept. Therefore, CellCept is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

Cyclosporine: Cyclosporine (Sandimmune®) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in ten stable

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

renal transplant patients. The mean (\pm SD) AUC_{0-12} and C_{max} of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 (\pm 822) ng·h/mL and 753 (\pm 161) ng/mL, respectively, compared to 3245 (\pm 1088) ng·h/mL and 700 (\pm 246) ng/mL, respectively, 1 week before administration of mycophenolate mofetil. The effect of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in this study; however, plasma concentrations of MPA were similar to that for healthy volunteers.

Ganciclovir: Following single-dose administration to twelve stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and IV ganciclovir (5 mg/kg). Mean (\pm SD) ganciclovir AUC and C_{max} (n=10) were 54.3 (\pm 19.0) μ g·h/mL and 11.5 (\pm 1.8) μ g/mL, respectively, after coadministration of the two drugs, compared to 51.0 (\pm 17.0) μ g·h/mL and 10.6 (\pm 2.0) μ g/mL, respectively, after administration of IV ganciclovir alone. The mean (\pm SD) AUC and C_{max} of MPA (n=12) after coadministration were 80.9 (\pm 21.6) μ g·h/mL and 27.8 (\pm 13.9) μ g/mL, respectively, compared to values of 80.3 (\pm 16.4) μ g·h/mL and 30.9 (\pm 11.2) μ g/mL, respectively, after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the potential exists for the two drugs to compete for tubular secretion and thus further increases in concentrations of both drugs may occur.

Oral Contraceptives: Following single-dose administration to fifteen healthy women, no pharmacokinetic interaction was observed between mycophenolate mofetil (1 g) and two tablets of Ortho-Novum® 7/7/7 (1 mg norethindrone [NET] and 35 μ g estradiol ethinyl [EE]). This single-dose study suggests the lack of a gross pharmacokinetic interaction, but cannot exclude the possibility of changes in the pharmacokinetics of the oral contraceptive under long-term dosing conditions with CellCept, which might adversely affect the efficacy of the oral contraceptive.

Trimethoprim/sulfamethoxazole: Following single-dose administration of mycophenolate mofetil (1.5 g) to twelve healthy male volunteers on day 8 of a 10 day course of Bactrim™ DS (trimethoprim 160 mg/sulfamethoxazole 800 mg) administered bid, no effect on the bioavailability of MPA was observed. The mean (\pm SD) AUC and C_{max} of MPA after concomitant administration were 75.2 (\pm 19.8) μ g·h/mL and 34.0 (\pm 6.6) μ g/mL, respectively, compared to 79.2 (\pm 27.9) and 34.2 (\pm 10.7), respectively, after administration of mycophenolate mofetil alone.

Other Interactions: The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, coadministration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil in monkeys results in a three-fold increase in plasma MPAG AUC and a two-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion.

Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil in daily doses up to 180 mg/kg was not tumorigenic. The highest dose tested was 0.5 times the recommended clinical dose (2 g/day) in renal transplant patients and 0.3 times the recommended clinical dose (3 g/day) in cardiac transplant patients when corrected for differences in body surface area (BSA). In a 104-week oral carcinogenicity study in rats, mycophenolate mofetil in daily doses up to 15 mg/kg was not tumorigenic. The highest dose was 0.08 times the recommended clinical dose in renal transplant patients and 0.05 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. While these animal doses were lower than those given to patients, they were maximal in those species and were considered adequate to evaluate the potential for human risk (see WARNINGS).

Mycophenolate mofetil was not genotoxic, with or without metabolic activation, in several assays: the bacterial mutation assay, the yeast mitotic gene conversion assay, the mouse micronucleus aberration assay, or the Chinese hamster ovary cell (CHO) chromosomal aberration assay.

Mycophenolate mofetil had no effect on fertility of male rats at oral doses up to 20 mg/kg/day. This dose represents 0.1 times the recommended clinical dose in renal transplant patients and 0.07 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. No effects on fertility or reproductive parameters were evident in the dams or in the subsequent generation.

Pregnancy: Category C. In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day and in rabbits at 90 mg/kg/day, in the absence of maternal toxicity. These levels are equivalent to 0.03 to 0.92 times the recommended clinical dose in renal transplant patients and 0.02 to 0.61 times the recommended clinical dose in cardiac transplant patients on a BSA basis. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

There are no adequate and well-controlled studies in pregnant women. CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. Effective contraception must be used before beginning CellCept therapy, during therapy and for 6 weeks after CellCept has been stopped (see WARNINGS, PRECAUTIONS: *Information for Patients*).

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Nursing Mothers: Studies in rats treated with mycophenolate mofetil have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from mycophenolate mofetil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients: Safety and effectiveness in pediatric patients have not been established. Very limited pharmacokinetic data are available in pediatric patients (see CLINICAL PHARMACOLOGY: *Pharmacokinetics*).

ADVERSE REACTIONS: The principal adverse reactions associated with the administration of CellCept include diarrhea, leukopenia, sepsis and vomiting, and there is evidence of a higher frequency of certain types of infections. The adverse event profile associated with the administration of CellCept Intravenous has been shown to be similar to that observed after administration of oral dosage forms of CellCept.

CellCept (oral): The incidence of adverse events for CellCept was determined in three randomized, comparative, double-blind trials in prevention of rejection in renal transplant patients, and in one randomized, comparative, double-blind trial in cardiac transplant patients.

Safety data are summarized below for all renal transplant patients in the double-blind prevention studies; approximately 53% of these patients have been treated for more than 1 year. Adverse events that were reported in $\geq 10\%$ of patients in either CellCept treatment group are presented below for the two active-controlled studies combined (USA and Europe/Canada/Australia) and for the one European placebo-controlled study. Because of the lower overall reporting of events in the European placebo-controlled study, these data were not combined with the other two active-controlled prevention trials, but are instead presented separately.

Adverse Events in Controlled Studies in Prevention of Renal Allograft Rejection

USA Study Combined with Europe/Canada/Australia Study

	CellCept 2 g/day (n=336)	CellCept 3 g/day (n=330)	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day (n=326)
<u>Body as a Whole</u>			
Pain	33.0%	31.2%	32.2%
Abdominal pain	24.7%	27.6%	23.0%
Fever	21.4%	23.3%	23.3%
Headache	21.1%	16.1%	21.2%
Infection	18.2%	20.9%	19.9%

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

USA Study Combined with Europe/Canada/Australia Study

	CellCept 2 g/day (n=336)	CellCept 3 g/day (n=330)	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day (n=326)
Sepsis	17.6%	19.7%	15.6%
Asthenia	13.7%	16.1%	19.9%
Chest pain	13.4%	13.3%	14.7%
Back pain	11.6%	12.1%	14.1%
<u>Hemic and Lymphatic</u>			
Anemia	25.6%	25.8%	23.6%
Leukopenia	23.2%	34.5%	24.8%
Thrombocytopenia	10.1%	8.2%	13.2%
Hypochromic anemia	7.4%	11.5%	9.2%
Leukocytosis	7.1%	10.9%	7.4%
<u>Urogenital</u>			
Urinary tract infection	37.2%	37.0%	33.7%
Hematuria	14.0%	12.1%	11.3%
Kidney tubular necrosis	6.3%	10.0%	5.8%
<u>Cardiovascular</u>			
Hypertension	32.4%	28.2%	32.2%
<u>Metabolic and Nutritional</u>			
Peripheral edema	28.6%	27.0%	28.2%
Hypercholesteremia	12.8%	8.5%	11.3%
Hypophosphatemia	12.5%	15.8%	11.7%
Edema	12.2%	11.8%	13.5%
Hypokalemia	10.1%	10.0%	8.3%
Hyperkalemia	8.9%	10.3%	16.9%
Hyperglycemia	8.6%	12.4%	15.0%
<u>Digestive</u>			
Diarrhea	31.0%	36.1%	20.9%
Constipation	22.9%	18.5%	22.4%
Nausea	19.9%	23.6%	24.5%
Dyspepsia	17.6%	13.6%	13.8%
Vomiting	12.5%	13.6%	9.2%
Nausea and vomiting	10.4%	9.7%	10.7%
Oral moniliasis	10.1%	12.1%	11.3%

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

USA Study Combined with Europe/Canada/Australia Study

	CellCept 2 g/day (n=336)	CellCept 3 g/day (n=330)	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day (n=326)
<u>Respiratory</u>			
Infection	22.0%	23.9%	19.6%
Dyspnea	15.5%	17.3%	16.6%
Cough increased	15.5%	13.3%	15.0%
Pharyngitis	9.5%	11.2%	8.0%
<u>Skin and Appendages</u>			
Acne	10.1%	9.7%	6.4%
Rash	7.7%	6.4%	10.4%
<u>Nervous System</u>			
Tremor	11.0%	11.8%	12.3%
Insomnia	8.9%	11.8%	10.4%
Dizziness	5.7%	11.2%	11.0%

Europe Study

	CellCept 2 g/day (n=165)	CellCept 3 g/day (n=160)	Placebo (n=166)
<u>Body as a Whole</u>			
Sepsis	21.8%	17.5%	13.9%
Infection	12.7%	15.6%	13.3%
Abdominal pain	12.1%	11.9%	11.4%
<u>Hemic and Lymphatic</u>			
Leukopenia	11.5%	16.3%	4.2%
<u>Urogenital</u>			
Urinary tract infection	45.5%	44.4%	37.3%
Urinary tract disorder	6.7%	10.6%	4.2%
<u>Cardiovascular</u>			
Hypertension	17.6%	16.9%	19.3%
<u>Digestive</u>			

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Diarrhea	16.4%	18.8%	13.9%
----------	-------	-------	-------

Respiratory

Infection	15.8%	13.1%	9.0%
Bronchitis	8.5%	11.9%	8.4%
Pneumonia	3.6%	10.6%	10.8%

In the randomized, double-blind, comparative trial in cardiac transplant recipients, approximately 65% of patients have been treated for more than 1 year. Adverse events reported in $\geq 10\%$ of patients in the group treated with CellCept are provided below.

Adverse Events in the Controlled Study in Prevention of Cardiac Allograft Rejection

	CellCept 3 g/day (n=289)	Azathioprine 1.5 to 3 mg/kg/day (n=289)
<u>Body as a Whole</u>		
Pain	75.8%	74.7%
Abdominal pain	33.9%	33.2%
Fever	47.4%	46.4%
Headache	54.3%	51.9%
Infection	25.6%	19.4%
Sepsis	18.7%	18.7%
Asthenia	43.3%	36.3%
Chest pain	26.3%	26.0%
Back pain	34.6%	28.4%
Accidental injury	19.0%	14.9%
Chills	11.4%	11.4%
<u>Hemic and Lymphatic</u>		
Anemia	42.9%	43.9%
Leukopenia	30.4%	39.1%
Thrombocytopenia	23.5%	27.0%
Hypochromic anemia	24.6%	23.5%
Leukocytosis	40.5%	35.6%
Ecchymosis	16.6%	8.0%
<u>Urogenital</u>		
Urinary tract infection	13.1%	11.8%
Kidney function abnormal	21.8%	26.3%
Oliguria	14.2%	12.8%
<u>Cardiovascular</u>		

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

	CellCept 3 g/day (n=289)	Azathioprine 1.5 to 3 mg/kg/day (n=289)
Hypertension	77.5%	72.3%
Hypotension	32.5%	36.0%
Cardiovascular disorder	25.6%	24.2%
Tachycardia	20.1%	18.0%
Arrhythmia	19.0%	18.7%
Bradycardia	17.3%	17.3%
Pericardial effusion	15.9%	13.5%
Heart failure	11.8%	8.7%

Metabolic and Nutritional

Peripheral edema	64.0%	53.3%
Hypercholesteremia	41.2%	38.4%
Edema	26.6%	25.6%
Hypokalemia	31.8%	25.6%
Hyperkalemia	14.5%	19.7%
Hyperglycemia	46.7%	52.6%
Creatinine increased	39.4%	36.0%
BUN increased	34.6%	32.5%
Lactic dehydrogenase increased	23.2%	17.0%
Bilirubinemia	18.0%	21.8%
Hypervolemia	16.6%	22.8%
Generalized edema	18.0%	20.1%
Hyperuricemia	16.3%	17.6%
SGOT increased	17.3%	15.6%
Hypomagnesemia	18.3%	12.8%
Acidosis	14.2%	16.6%
Weight gain	15.6%	15.2%
SGPT increased	15.6%	12.5%
Hyponatremia	11.4%	11.8%
Hyperlipemia	10.7%	9.3%

Digestive

Diarrhea	45.3%	34.3%
Constipation	41.2%	37.7%
Nausea	54.0%	54.3%
Dyspepsia	18.7%	19.4%
Vomiting	33.9%	28.4%
Nausea and vomiting	11.1%	7.6%
Oral moniliasis	11.4%	11.8%
Flatulence	13.8%	15.6%

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

	CellCept 3 g/day (n=289)	Azathioprine 1.5 to 3 mg/kg/day (n=289)
<u>Respiratory</u>		
Infection	37.0%	35.3%
Dyspnea	36.7%	36.3%
Cough increased	31.1%	25.6%
Pharyngitis	18.3%	13.5%
Lung disorder	30.1%	29.1%
Sinusitis	26.0%	19.0%
Rhinitis	19.0%	15.6%
Pleural effusion	17.0%	13.8%
Asthma	11.1%	11.4%
Pneumonia	10.7%	10.4%
<u>Skin and Appendages</u>		
Acne	12.1%	9.3%
Rash	22.1%	18.0%
Skin disorder	12.5%	8.7%
<u>Nervous System</u>		
Tremor	24.2%	23.9%
Insomnia	40.8%	37.7%
Dizziness	28.7%	27.7%
Anxiety	28.4%	23.9%
Paresthesia	20.8%	18.0%
Hypertonia	15.6%	14.5%
Depression	15.6%	12.5%
Agitation	13.1%	12.8%
Somnolence	11.1%	10.4%
Confusion	13.5%	7.6%
Nervousness	11.4%	9.0%
<u>Musculoskeletal System</u>		
Leg Cramps	16.6%	15.6%
Myasthenia	12.5%	9.7%
Myalgia	12.5%	9.3%
<u>Special Senses</u>		
Amblyopia	14.9%	6.6%
<u>Endocrine System</u>		
	12.1%	12.8%

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

The above data demonstrate that in three controlled trials for prevention of renal rejection, patients receiving 2 g/day of CellCept had an overall better safety profile than did patients receiving 3 g/day of CellCept. Sepsis, which was generally CMV viremia, was slightly more common in those renal patients treated with CellCept, with an incidence of 18% to 22%, compared to 16% in patients receiving azathioprine and 14% in patients receiving placebo. In the controlled cardiac transplant study, there was no difference in the incidence of sepsis (18.7%) between patients treated with CellCept and control patients. In the digestive system, diarrhea was increased in renal and cardiac patients receiving CellCept, with an incidence of up to 36%, compared to 21% for patients receiving azathioprine and 14% for patients receiving placebo in the renal transplant studies. In the controlled cardiac transplant study, an incidence of diarrhea up to 45.3% in the patients treated with CellCept was reported compared to 34.3% for patients receiving azathioprine. The types of adverse events in the cardiac transplant patients studied in the multicenter controlled trial were qualitatively similar to those observed in renal transplant patients.

The incidence of malignancies among the 1483 patients treated in controlled trials for the prevention of renal allograft rejection who were followed for ≥ 1 year was similar to the incidence reported in the literature for renal allograft recipients. Lymphoproliferative disease or lymphoma developed in approximately 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal and cardiac transplant patients (see WARNINGS). The following table summarizes the incidence of malignancies observed in the controlled renal and cardiac trials.

Malignancies Observed in Renal and Cardiac Transplant Trials

	Renal Trials				Cardiac Trial	
	CellCept 2 g/day (n=501)	CellCept 3 g/day (n=490)	Placebo (n=166)	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day (n=326)	CellCept 3 g/day (n=289)	Azathioprine 1.5 to 3 mg/kg/day (n=289)
Lymphoma/ lymphoprolifera- tive disease	0.6%	1.0%	0.0%	0.3%	0.7%	2.1%
Non-melanoma skin carcinoma	4.0%	1.6%	0.0%	2.4%	4.2%	2.8%
Other malignancy	0.8%	1.4%	1.8%	1.8%	2.1%	2.1%

Up to 2.0% of patients receiving CellCept 3 g daily for prevention of renal rejection developed severe neutropenia [absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu\text{L}$]. Up to 2.8% of cardiac transplant patients receiving CellCept 3 g daily developed severe neutropenia (see WARNINGS, PRECAUTIONS: *Laboratory Tests* and DOSAGE AND ADMINISTRATION).

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

The following tables show the incidence of opportunistic infections that occurred in the renal and cardiac transplant populations in the controlled prevention trials:

Opportunistic Infections in Prevention of Renal Rejection Trials

USA Study Combined with Europe/Canada/Australia Study

	CellCept 2 g/day (n=336)	CellCept 3 g/day (n=330)	Azathioprine 1 to 2 mg/kg/day or 100 to 150 mg/day (n=326)
Herpes simplex	16.7%	20.0%	19.0%
CMV			
viremia/syndrome	13.4%	12.4%	13.8%
tissue invasive disease	8.3%	11.5%	6.1%
Herpes zoster	6.0%	7.6%	5.8%
Candida			
fungemia/disseminated	0.6%	0.6%	0.3%
tissue invasive disease	0.6%	0.6%	0.3%
Aspergillus/Mucor invasive disease	0.3%	0.9%	0.3%
Pneumocystis carinii	0.3%	0.0%	1.2%

Europe Study

	CellCept 2 g/day (n=165)	CellCept 3 g/day (n=160)	Placebo (n=166)
Herpes simplex	15.2%	12.5%	6.0%
CMV			
viremia/syndrome	15.2%	15.0%	13.3%
tissue invasive disease	3.6%	7.5%	2.4%
Herpes zoster	6.7%	6.9%	2.4%
Candida			
fungemia/disseminated	0.0%	0.6%	0.0%
tissue invasive disease	0.0%	0.6%	0.0%
Pneumocystis carinii	0.0%	0.0%	2.4%

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Opportunistic Infections in Prevention of Cardiac Rejection Trial

	CellCept 3 g/day (n=289)	Azathioprine 1.5 to 3 mg/kg/day (n=289)
Herpes simplex	20.8%	14.5%
CMV		
viremia/syndrome	12.1%	10.0%
tissue invasive disease	11.4%	8.7%
CMV infection	2.8%	2.8%
CMV urine	2.4%	2.8%
CMV nasal secretions	0.3%	0.0%
CMV saliva	0.3%	0.0%
Herpes zoster	10.7%	5.9%
Herpes zoster cutaneous disease	10.0%	5.5%
Herpes zoster visceral disease	0.7%	0.3%
Candida	18.7%	17.6%
mucocutaneous	18.0%	17.3%
urinary tract infection	0.7%	1.0%
fungemia/disseminated disease	0.7%	0.3%
invasive tissue disease	0.0%	0.3%
Cryptococcosis	0.7%	0.3%
Aspergillus/Mucor	2.1%	2.1%
Aspergillus pulmonary or sinus invasive	0.7%	1.4%
Aspergillus disseminated or metastatic	0.3%	1.0%
Aspergillus cutaneous	0.7%	0.0%
Aspergillus sputum	0.3%	0.3%
Pneumocystis carinii	0.0%	1.7%
Listeriosis	0.0%	0.7%

In controlled studies for prevention of renal or cardiac rejection, similar rates of fatal infection/sepsis (<2%) occurred in patients receiving CellCept (2 g or 3 g) (see WARNINGS). In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept than in those receiving azathioprine, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

The following adverse events, not mentioned in any of the tables above, were reported with $\geq 3\%$ incidence in both renal and cardiac transplant patients treated with CellCept, in combination with cyclosporine and corticosteroids.

Body as a Whole: abdomen enlarged, chills occurring with fever, cyst, face edema, flu syndrome, hemorrhage, pelvic pain, malaise

Urogenital: dysuria, impotence, urinary frequency

Cardiovascular: angina pectoris, atrial fibrillation, palpitation, peripheral vascular disorder, postural hypotension

Metabolic and Nutritional: alkaline phosphatase increased, dehydration, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia

Digestive: anorexia, esophagitis, gastritis, gastroenteritis, gingivitis, gum hyperplasia, infection, liver function tests abnormal, rectal disorder

Respiratory: lung edema

Skin and Appendages: fungal dermatitis, pruritus, skin benign neoplasm, skin hypertrophy, skin ulcer, sweating

Endocrine: diabetes mellitus

Musculoskeletal: arthralgia, joint disorder

Special Senses: conjunctivitis

The following adverse events, not mentioned in any of the tables above were reported with $\geq 3\%$ incidence in renal transplant patients only treated with CellCept, in combination with other immunosuppressive agents:

Body as a Whole: accidental injury, hernia

Hemic and Lymphatic: ecchymosis, polycythemia

Urogenital: albuminuria, hydronephrosis, pain, pyelonephritis, urinary tract disorder

Cardiovascular: cardiovascular disorder, hypotension, tachycardia, thrombosis, vasodilatation

Metabolic and Nutritional: acidosis, creatinine increased, gamma glutamyl transpeptidase increased, hypercalcemia, hyperlipemia, hyperuricemia, lactic dehydrogenase increased, SGOT increased, SGPT increased, weight gain

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Digestive: flatulence, gastrointestinal hemorrhage, gastrointestinal moniliasis, hepatitis, ileus, mouth ulceration

Respiratory: asthma, lung disorder, pleural effusion, rhinitis, sinusitis

Skin and Appendages: alopecia, hirsutism, rash, skin disorder

Nervous: anxiety, depression, hypertonia, paresthesia, somnolence

Endocrine: parathyroid disorder

Musculoskeletal: leg cramps, myalgia, myasthenia

Special Senses: amblyopia, cataract (not specified)

The following adverse events, not mentioned in any of the tables above, were reported with $\geq 3\%$ incidence in cardiac transplant patients treated with CellCept, in combination with other immunosuppressive agents:

Body as a Whole: neck pain, cellulitis

Hemic and Lymphatic: prothrombin increased, thromboplastin decreased, petechia

Urogenital: nocturia, kidney failure, urine abnormality, hematuria, urinary incontinence, prostatic disorder, urinary retention

Cardiovascular: ventricular extrasystole, congestive heart failure, supraventricular tachycardia, ventricular tachycardia, atrial flutter, pulmonary hypertension, heart arrest, venous pressure increased, syncope, supraventricular extrasystoles, extrasystoles, pallor, vasospasm

Metabolic and Nutritional: hypoxia, hypophosphatemia, gout, abnormal healing, alkalosis, weight loss, hypochloremia, thirst, respiratory acidosis

Digestive: gastrointestinal disorder, melena, liver damage, dysphagia, jaundice, stomatitis

Respiratory: atelectasis, hiccup, pneumothorax, sputum increased, respiratory disorder, epistaxis, apnea, voice alteration, pain, hemoptysis, neoplasm

Skin and Appendages: hemorrhage, skin carcinoma

Nervous: emotional lability, neuropathy, convulsion, hallucinations, thinking abnormal, vertigo

Endocrine: Cushing's syndrome, hypothyroidism

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Special Senses: ear pain, deafness, ear disorder, tinnitus, abnormal vision, lacrimation disorder, eye hemorrhage

CellCept Intravenous: The adverse event profile of CellCept Intravenous was determined from a single, double-blind, controlled comparative study of the safety of 2 g/day of intravenous and oral CellCept in the immediate posttransplant period (administered for the first 5 days). The potential venous irritation of CellCept Intravenous was evaluated by comparing the adverse events attributable to peripheral venous infusion of CellCept Intravenous with those observed in the IV placebo group; patients in this group received active medication by the oral route.

Adverse events attributable to peripheral venous infusion were phlebitis and thrombosis, both observed at 4% in patients treated with CellCept Intravenous.

Postmarketing Experience

Digestive: colitis (sometimes caused by cytomegalovirus), pancreatitis

Resistance Mechanism Disorders: Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection.

OVERDOSAGE: There has been no reported experience of overdosage of mycophenolate mofetil in humans. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea, vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 4000 mg/kg or in adult monkeys at doses up to 1000 mg/kg; these were the highest doses of mycophenolate mofetil tested in these species. These doses represent 11 times the recommended clinical dose in renal transplant patients and approximately 7 times the recommended clinical dose in cardiac transplant patients when corrected for BSA. In adult rats, deaths occurred after single oral doses of 500 mg/kg of mycophenolate mofetil. The dose represents approximately 3 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.

MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

DOSAGE AND ADMINISTRATION: RENAL TRANSPLANTATION: A dose of 1.0 g administered orally or intravenously (over 2 hours) twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. Although a dose of 1.5 g administered twice daily (daily dose of 3 g) was used in clinical trials and was shown to be safe and effective, no efficacy advantage could be established for renal transplant patients. Patients receiving 2 g/day of CellCept demonstrated an overall better safety profile than did patients receiving 3 g/day of CellCept.

CARDIAC TRANSPLANTATION: A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in cardiac transplant patients.

CellCept Capsules, Tablets and Oral Suspension: The initial oral dose of CellCept should be given as soon as possible following renal or cardiac transplantation. Food had no effect on MPA AUC, but has been shown to decrease MPA C_{max} by 40%. Therefore, it is recommended that CellCept be administered on an empty stomach.

Note

If required CellCept Oral Suspension can be administered via a nasogastric tube with a minimum size of 8 French (minimum 1.7 mm interior diameter).

Preparation of Suspension

It is recommended that CellCept Oral Suspension be constituted by the pharmacist prior to dispensing to the patient.

Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits. There are no adequate and well controlled studies in pregnant women. (See WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and HANDLING AND DISPOSAL). Care should be taken to avoid inhalation or direct contact with skin or mucous membranes of the dry powder or the constituted suspension. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water.

1. Tap the closed bottle several times to loosen the powder.
2. Measure 94 mL of water in a graduated cylinder.
3. Add approximately half the total amount of water for constitution to the bottle and shake the closed bottle well for about 1 minute.
4. Add the remainder of water and shake the closed bottle well for about 1 minute.
5. Remove the child-resistant cap and push bottle adapter into neck of bottle.
6. Close bottle with child-resistant cap tightly. This will assure the proper seating of the bottle adapter in the bottle and child-resistant status of the cap

Dispense with patient instruction sheet and oral dispensers. It is recommended to write the date of expiration of the constituted suspension on the bottle label. (The shelf-life of the constituted suspension is 60 days.)

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

After constitution the oral suspension contains 200 mg/mL mycophenolate mofetil. Store constituted suspension at 25° C (77° F); excursions permitted to 15° to 30°C (59° to 86°F). Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable. Do not freeze. Discard any unused portion 60 days after constitution.

CellCept Intravenous: CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension recommended for patients unable to take oral CellCept. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

CellCept Intravenous must be reconstituted and diluted to a concentration of 6 mg/mL using 5% Dextrose Injection USP. CellCept Intravenous is incompatible with other intravenous infusion solutions. Following reconstitution, CellCept Intravenous must be administered by slow intravenous infusion over a period of NO LESS THAN 2 HOURS by either peripheral or central vein.

CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION.

Preparation of Infusion Solution (6 mg/mL):

Caution should be exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid skin contact of the solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. (See WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and HANDLING AND DISPOSAL).

CellCept Intravenous does not contain an antibacterial preservative; therefore, reconstitution and dilution of the product must be performed under aseptic conditions.

CellCept Intravenous infusion solution must be prepared in two steps: the first step is a reconstitution step with 5% Dextrose Injection, USP and the second step is a dilution step with 5% Dextrose Injection, USP. A detailed description of the preparation is given below:

Step 1

- a. Two (2) vials of CellCept Intravenous are used for preparing each 1 g dose, whereas three (3) vials are needed for each 1.5 g dose. Reconstitute the contents of each vial by injecting 14 mL of 5% Dextrose Injection, USP.
- b. Gently shake the vial to dissolve the drug.
- c. Inspect the resulting slightly yellow solution for particulate matter and discoloration prior to further dilution. Discard the vial if particulate matter or discoloration is observed.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

Step 2

- a. To prepare a 1 g dose, further dilute the contents of the two reconstituted vials (approx. 2 x 15 mL) into 140 mL of 5% Dextrose Injection USP. To prepare a 1.5 g dose, further dilute the contents of the three reconstituted vials (approx. 3 x 15 mL) into 210 mL of 5% Dextrose Injection USP. The final concentration of both solutions is 6 mg mycophenolate mofetil per mL.
- b. Inspect the infusion solution for particulate matter or discoloration. Discard the infusion solution if particulate matter or discoloration is observed.

If the infusion solution is not prepared immediately prior to administration, the commencement of administration of the infusion solution should be within 4 hours from reconstitution and dilution of the drug product. Keep solutions at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

CellCept Intravenous should not be mixed or administered concurrently via the same infusion catheter with other intravenous drugs or infusion admixtures.

Dosage Adjustments: In renal transplant patients with severe chronic renal impairment (GFR <25 mL/min/1.73m²) outside of the immediate posttransplant period, doses of CellCept greater than 1 g administered twice a day should be avoided. These patients should also be carefully observed. No dose adjustments are needed in renal transplant patients experiencing delayed graft function postoperatively (see CLINICAL PHARMACOLOGY: *Pharmacokinetics* and PRECAUTIONS: *General*).

No data are available for cardiac transplant patients with severe chronic renal impairment. CellCept may be used for cardiac transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

If neutropenia develops (ANC <1.3 x 10³/μL), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see WARNINGS, ADVERSE REACTIONS, and PRECAUTIONS: *Laboratory Tests*).

HANDLING AND DISPOSAL: Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits. CellCept tablets should not be crushed and CellCept capsules should not be opened or crushed. Avoid inhalation or direct contact with skin or mucous membranes of the powder contained in CellCept capsules and CellCept Oral Suspension (before or after constitution). If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water. Should a spill occur wipe up using paper towels wetted with water to remove spilled powder or suspension. Caution should be exercised in the handling and preparation of solutions of CellCept Intravenous. Avoid skin contact of the solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with plain water.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

HOW SUPPLIED:

CellCept (mycophenolate mofetil capsules)

250 mg

Blue-brown, two-piece hard gelatin capsules, printed in black with "CellCept 250" on the blue cap and "Roche" on the brown body. Supplied in the following presentations:

<u>NDC Number</u>	<u>Size</u>
NDC 0004-0259-01	Bottle of 100
NDC 0004-0259-43	Bottle of 500

Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

CellCept (mycophenolate mofetil tablets)

500 mg

Lavender-colored, caplet-shaped, film-coated tablets printed in black with "CellCept 500" on one side and "Roche" on the other. Supplied in the following presentations:

<u>NDC Number</u>	<u>Size</u>
NDC 0004-0260-01	Bottle of 100
NDC 0004-0260-43	Bottle of 500

Storage and Dispensing Information: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Dispense in light-resistant containers, such as the manufacturer's original containers.

CellCept Oral Suspension (mycophenolate mofetil for oral suspension)

Supplied as a white to off-white powder blend for constitution to a white to off-white mixed-fruit flavor suspension. Supplied in the following presentation:

<u>NDC Number</u>	<u>Size</u>
NDC 0004-0261-29	225 mL bottle with bottle adapter and 2 oral dispensers

Storage:

Store dry powder at 25° C (77° F); excursions permitted to 15° to 30°C (59° to 86°F).

Store constituted suspension at 25° C (77° F); excursions permitted to 15° to 30°C (59° to 86°F) for up to 60 days. Storage in a refrigerator at 2° to 8°C (36° to 46°F) is acceptable. Do not freeze.

CellCept® (mycophenolate mofetil capsules)

CellCept® (mycophenolate mofetil tablets)

CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection)

CellCept Intravenous (mycophenolate mofetil hydrochloride for injection)

Supplied in a 20 mL, sterile vial containing the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt in cartons of 4 vials:

NDC Number

NDC 0004-0298-09

Storage: Store powder and reconstituted/infusion solutions at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

CAUTION: Federal (USA) law prohibits dispensing without a prescription.

CellCept capsules and tablets manufactured by: Syntex Puerto Rico, Inc., Humacao, Puerto Rico 00791

CellCept Intravenous manufactured by: Parkedale Pharmaceuticals, Inc., 870 Parkdale Road, Rochester, Michigan 48307

for:

(Roche Hexagon)

Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

26271004-0898

Revised: September 1998

Copyright © 1998 by Roche Laboratories Inc. All rights reserved.